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Carroll No. 903

Warfarin and its Sodium Salt

[3-(alpha-Acetylbenzyl)-4-hydroxycoumarin]

PESTICIDE REGISTRATION STANDARD

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VI. Toxicology1. Toxicology Profile

Sodium warfarin ^{*/} has been used as an anticoagulant drug in humans since the late 1950's. An extensive body of literature has accumulated from this use. Information is available on dose and effect relationships, mechanism of action, spectrum of toxic effects and treatment of toxic effects. Detailed discussions of this data are found in all pharmacology and toxicology text books and a knowledge of warfarin's toxicity is part of the training of physicians. A working knowledge is necessary for all physicians treating cardio-vascular conditions. The Agency has, therefore, based its determinations relative to human safety in this Standard on this body of human evidence. Also included for information of the reader only is a discussion of specific registrant-submitted and some open-literature toxicity studies of warfarin. This data is summarized in Table VI-A.

2. Technical and Manufacturing-Use Productsa. Technical

General information on the oral toxicity of the sodium salt of warfarin to humans is readily available (Cosselin et al., 1976, GS0011-117; Meyers et al., 1978, GS0011-119; DiPalma, 1971, GS0011-121; Gilman et al., 1980, GS0011-122;).

Available estimates of the acute oral LD₅₀ of technical warfarin in animals vary considerably in the available literature (Table VI-A). The human data from the public literature suggest that technical warfarin may be highly toxic to humans (Gaines, 1960, 05002272; Back et al., 1978, 05003932; Hagan and Radomski, 1955, 05002258 -- see also Zendzian, 1981, GS0011-120).

Although an instance of human poisoning has been alledged to have resulted from the repeated careless use of a warfarin concentrate (Fristedt and Sterner, 1965, 05002245), no reports of toxicity following single exposures are available. A low dermal toxicity is expected (Category III) (Zendzian, 1981, GS0011-120). In studies with rabbits, the acute dermal toxicity of warfarin on intact skin was low (LD₅₀ greater than 3 g/kg) (Shapiro, 1976, 00002443).

No toxicity data were available to assess the acute inhalation toxicity of warfarin. Based upon the available data on the physical properties of warfarin, it is highly unlikely that warfarin would produce sufficient quantities of vapor to be toxic (Zendzian, 1981, GS0011-120).

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^{*/} There are essentially no toxicological differences between technical warfarin and sodium warfarin when adjustments are made for the relative purity of the individual batches of test material.

TABLE VI-A

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WARFARIN TOXICITY STUDIES

TEST/MATERIAL	ORGANISM	SEX	RESULTS	CITATION
ACUTE ORAL LD ₅₀				
- Technical Warfarin	Rat	M	3.0 mg/kg	Gaines, 1960, 05002272
- Technical Sodium Warfarin	Rat	M	112 mg/kg	Back et al., 1978, 05003932
		F	10.4 mg/kg	
- Technical Sodium Warfarin	Rat	M	100.3 mg/kg	Back et al., 1978, 05003932
		F	8.7 mg/kg	
- Technical Sodium Warfarin	Rat	M	323 mg/kg	Hagan and Radomski, 1953, 05002258
		F	58 mg/kg	
	Guinea Pig	M,F	182 mg/kg	"
	Mouse	M,F	374 mg/kg	"
	Rabbit	M,F	800 mg/kg	"
	Dog	M,F	200-300 mg/kg	"
	Chicken	M,F	>1 g/kg	"
- Technical Warfarin	Cats	-	2.5 - 20 mg/kg	Til et al., 1974, 00002461
- Warfarin	Rat	M	450-680 mg/kg	WARF, 1977, GS0011-106
		F	<10 mg/kg	
- Warfarin	Rat	F	2.5 - 5.0 mg/kg	WARF, 1977, GS0011-107
- Encapsulated Warfarin	Rat	M	12.5 mg/kg	WARF, 1977, GS0011-103
		F	1.2 - 2.5 mg/kg	
- Encapsulated Warfarin	Rat	M	32 mg/kg	WARF, 1977, GS0011-102
		F	<10 mg/kg	
- 5.4% Granular Warfarin	Rat	M,F	55 g/kg	Shapiro, 1977, 00002282
- 5.4% Granular Warfarin	Rat	M	<100 g/kg	Shapiro, 1977, 00002281
- 0.025% Bait	Rat	M,F	>20 g/kg	WARF, 1977, GS0011-113

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TABLE VI-A (CONTINUED)

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TEST/MATERIAL	ORGANISM	SEX	RESULTS	CITATION
ACUTE DERMAL LD ₅₀				
- Technical Warfarin	Rabbit	M,F	>8 g/kg	Shapiro, 1976, 00002443
- 5.4% Granular Warfarin	Rabbit	M,F	>20 g/kg	Shapiro, 1977, 00002280
- 0.025% Bait	Rabbit	F	>20 g/kg	WARF, 1977, GS0011-116
PRIMARY EYE IRRITATION				
- Warfarin	Rabbit	-	None	WARF, 1977, GS0011-104
- Technical Warfarin	Rabbit	-	Mild conjunctival irritation	Shapiro, 1976, 00003288
- Encapsulated Warfarin	Rabbit	-	None	WARF, 1977, GS0011-100
- Technical Warfarin	Rabbit	-	Slight conjunctival irritation	Shapiro, 1977, 00002430
- 0.54% Granular Warfarin	Rabbit	-	Conjunctival irritation	Shapiro, 1976, 00002852
- 0.025% Bait	Rabbit	-	None	WARF, 1977, GS0011-115
- 5.4% Granular Warfarin	Rabbit	-	Moderate to severe conjunctival irritation	Shapiro, 1977, 00002284
PRIMARY DERMAL IRRITATION				
- Warfarin	Rabbit	-	None	WARF, 1977, GS0011-105
- Technical Warfarin	Rabbit	-	None	Shapiro, 1976, 00002851
- Encapsulated Warfarin	Rabbit	-	None	WARF, 1977, GS0011-101
- 0.54% Warfarin	-	-	Mild dermal irritation at 24 hours	Shapiro, 1976, 00003287
- 5.4% Granular	-	-	Very slight dermal irritation at 24 hours	Shapiro, 1976, 00002283

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TABLE VI-A (CONTINUED)

TEST/MATERIAL	ORGANISM	SEX	RESULTS	CITATION
- 0.025% Bait	-	-	Very slight dermal irritation at 24 hours	Shapiro, 1976, 00003290
- 0.025% Bait	Rabbit	-	None	WARF, 1977, GS0011-114
TERATOGENICITY				
- Clinical Sodium Warfarin	Human	F	Fetal Abnormalities	Sherman and Hall, 1976, 05002097
- Clinical Sodium Warfarin	Human	F	"	Shaul et al., 1975, 05001852, 1975,
- Clinical Sodium Warfarin	Human	F	"	Warkany, 1976, 05001730
- Clinical Sodium Warfarin	Human	F	"	Holzgrevé et al., 1976, 05003388
CLINICAL EXPERIENCE				
- 0.25% Warfarin on corn meal	Human	M,F	2 fatalities after ingesting the meal over 15 days	Lange and Terveer, 1954, 05004097
EMERGENCY TREATMENT				
- Clinical Sodium Warfarin	Human	M,F	-	Gosselin et al., 1974, GS0011-117
"	"	"	-	Casarett and Doull, 1975, GS0011-118
"	"	"	-	Meyers et al., 1978, GS0011-119
"	"	"	-	Di Palma, 1971, GS0011-121
"	"	"	-	Gilman et al. 1980, GS0011-122

Warfarin has no chemical moieties capable of acidic or basic function and there are no reports of tissue damage following human use (including that by injection) of liquid warfarin. Human data and the chemistry of warfarin indicate a low potential for acute eye effects (Zendzian, 1981, GS0011-120). Primary eye irritation studies (one on technical warfarin, WARF, 1977, GS0011-104; one on encapsulated technical warfarin, WARF, 1977, GS0011-100) in animals indicated that this material was not an eye irritant while other studies indicated that technical warfarin produced mild to slight irritation of the conjunctive. Information on the concentration of warfarin used was not specified in these studies (Shapiro, 1976, 00002238; Shapiro, 1977, 00002230).

Despite extensive human use of warfarin, no reports of dermal inflammatory or allergic responses are available, therefore, warfarin's potential for causing acute dermal effects is judged to be low (Zendzian, 1981, GS0011-120). One animal study on an unspecified concentration of warfarin showed that it was not irritating to the intact skin of rabbits. In this study neither the concentration of warfarin nor the diluent of the study material were specified (Shapiro, 1976, 00002251). Two additional animal studies (one on technical warfarin, WARF, 1977, GS0011-105; one on encapsulated technical warfarin, WARF, 1977, GS0011-101) also indicated that this material was not a primary skin irritant. No data were available to assess the dermal sensitization potential of technical warfarin.

3. End-Use Products

Warfarin end-use products are usually formulated with inert agents such as silicone and mineral or food materials such as grain. The toxicity of these products is expected to be proportional to their warfarin content. All toxicity data requirements are satisfied by available clinical evidence associated with warfarin's human drug use. Other data are discussed below for the readers general information only.

a. Granular

One study indicated that the acute oral LD₅₀ of a 0.025% granular bait was greater than 20 g/kg for both male and female rats (WARF, 1977, GS0011-113). Additional acute oral toxicity studies are available on a granular formulation containing 5.4% warfarin (Shapiro, 1977, 00002282; Shapiro, 1977, 00002281).

One animal study of a 5.4% granular product indicated an acute dermal toxicity of greater than 20 g/kg (Shapiro, 1977, 00002280). An additional acute dermal toxicity study with 0.025% warfarin bait gave similar results (WARF, 1977, GS0011-115). In a primary eye irritation study, 0.1 ml of a 0.54%

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granular formulation produced conjunctival irritation in rabbits. The study did not report the concentration of warfarin used (Shapiro, 1977, 00002952). In another primary eye irritation study, (Shapiro, 1977, 00002284) 0.1 ml of a 5.4% granular formulation produced moderate to severe conjunctival irritation (the concentration of warfarin and the diluent of the test material used were not specified). Another primary eye irritation study indicated that a 0.025% warfarin bait was negative in this regard (WARF, 1977, GS0011-115). Because of the characteristics of the solid granular materials mixed with some warfarin formulations, these products would be expected to physically irritate the eye.

In a primary dermal irritation study, 0.5 ml of a granular formulation produced very slight dermal irritation at 24 hours. The concentration of warfarin used was not specified in this study (Shapiro, 1977, 00002223). In a primary dermal irritation test, 0.5ml of a 0.54% granular formulation produced mild dermal irritation at 24 hours. This study did not indicate the concentration of warfarin used (Shapiro, 1976, 00003237). One other primary skin irritation study with a 0.025% bait indicated that this material was negative in this regard (WARF, 1977, GS0011-114).

In a primary dermal irritation study 0.5 ml of a pelleted/tableted formulation produced very slight dermal irritation at 24 hours. The concentration of warfarin and the diluent of the test material used were not reported (Shapiro, 1976, 00003290).

4. Toxicity Categories

An acute oral toxicity category of I for technical warfarin, is indicated by human data. Formulated products having 2% or less warfarin would have a much lower acute oral toxicity category. In addition, human data seem to indicate a toxicity category III for eye effects for technical warfarin and category IV for skin effects for technical warfarin. Human data indicate an acute dermal toxicity category of III for technical warfarin.

5. Human and Domestic Animal Hazard Assessment

A large data base exists for sodium warfarin as a result of its clinical use as an anticoagulant drug. These data clearly delineate the drug doses of sodium warfarin its effects its mechanism of action, and the treatment for poisoning by warfarin (Zendzian, 1981, GS0011-120). Data also indicate that warfarin is a weak teratogen, (Sherman and Hall, 1976, 05002097; Chaul et al., 1975, 05001853; Warkany, 1976, 05001730; Holzgreve et al., 1976, 05003339), and the FDA, therefore, requires the following label warning on products used during pregnancy:

Pregnancy - COUNADIN passes through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage in utero even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. The newborn may be particularly sensitive to sodium warfarin. There have been reports of birth malformations in children born to mothers who have been treated with warfarin during the first trimester of pregnancy. Whether warfarin was in fact the responsible agent has not been established. Therefore, women of childbearing potential who are candidates for anti-coagulant therapy should be carefully evaluated and the

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indications critically reviewed. If COUMADIN must be used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

The Agency finds this statement to be a reasonable summary of the scientific data on warfarin's teratogenic potential in humans.

The Agency believes that a label warning against exposure of pregnant females is appropriate on manufacturing-use warfarin products. Registrants who disagree with this assessment must supply the Agency with data regarding warfarin's teratogenic potential.

Some warfarin products contain sulfaquinoxaline as an additional active ingredient. The Agency has determined that data do not show sulfaquinoxaline to be an efficacious active rodenticidal ingredient (see page II-1 and Chapter IX). Additionally, data are not available to allow the Agency to determine whether sulfaquinoxaline presents a risk to humans. Therefore, the Agency will require registrants who wish to retain this ingredient in their formulations to perform a test on technical sulfaquinoxaline to determine its acute oral LD₅₀ and if it is found to be acutely toxic, registrants will be required to perform, in addition, all acute toxicology tests required by the guidelines.

6. Summary of Major Data Gaps

An acute inhalation toxicity test is required for warfarin. In addition, at least an acute oral LD₅₀ test will have to be performed on sulfaquinoxaline (additional basic acute toxicity tests will be required for sulfaquinoxaline if it is found to be acutely toxic by the oral route).

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